

May 9, 1967

Jack P. Strong, M.D.
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Dear Doctor Strong:

I have been planning to write to you ever since our visit last January, about the several items in my notes. Your letter now provides the stimulus to take action.

Acetonitrile

Most of what has been done on this is not yet published and we think that considerably more chemical work is still needed to validate the methodology and especially to solve the problems of kinetics in absorption and excretion. Studies on the subject were initiated at the Southwest Research Institute in San Antonio under government contracts and then continued under a grant from this Council. Before the work was completed, the man who was most concerned with it made a move. We have just received a "final" report but this leaves many loose ends. Under separate cover, we are sending you copies of the brief notes that have been published and excerpts from the reports we have. These are to be considered confidential and, as you will see, do not add up to a validated method ready for routine application. If you wish to get into this subject, it will require some constructive thinking and further research. The material is intended to save time and assist in research into applicability rather than as a description of a tested methodology.

Inhalation Studies

I think you have received a copy of our Annual Report for 1965-1966. On pages 11-13 you will find a report of our conference on techniques for exposure of experimental animals to cigarette smoke inhalation, including a statement of the conditions that we feel must be met to make such work really useful in describing dose-response relationships. Until there is some satisfactory method for controlling and estimating the actual lung surface exposures to the particulate and gas plus vapor phases of smoke, attempts to relate specific histopathological changes to dosage will remain rather vaguely qualitative. We are concentrating on these problems at present and have made some progress insofar as small animals are concerned. Small rodents, however, have not been used very much for studies of the cardiovascular system and, so far as I know, there is little background on the processes of arteriosclerosis in such animals.

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We are just now undertaking an inhalation study with dogs to work out better methodology. We have not tackled primates along these lines. They will surely present a more difficult problem because of their manual dexterity.

For these reasons, I am sure our Board members feel that spontaneous smoking by baboons can, at present, contribute in a meaningful manner rather to study of psychological and motivational phenomena than to physiological, pathological or biochemical ones.

Atherosclerosis studies

The possibility of using primates, especially smaller ones, as a model for atherosclerosis studies seems more promising for the immediate future. If conditions can be established for producing lesions closely resembling the human ones, in a consistent and reproducible manner, it might be possible to superimpose chronic nicotine dosages (in water, food, pills or by injection) at several levels for observation of any differences induced by the alkaloid.

It would actually be much more interesting to superimpose whole smoke inhalation upon the atherogenic regimen, but the methodology for this seems not yet to be at hand. Even more interesting, perhaps, would be superimposed inhalation of the gas phase of smoke or of certain constituents, especially carbon monoxide (see Astrup). The last should be far easier experimentally since it would not involve the handling of a rapidly changing heterogeneous aerosol.

To make any such studies practical, we would need a basic atherogenic regime giving rather uniform effects so that we would not have to use unduly large numbers of animals.

Autopsy study

Among all the subjects we discussed, it seems most appropos to provide for continuation of your present autopsy study until a total of 1500 cases has been accumulated, and to continue analysis of data.

Arteries of young men, race relations.

This kind of thing undoubtedly ought to be done but I am uncertain as to how directly relevant to our purposes such studies will be considered by our Board.

Lung lipids

Since several studies on the effects of chronic influences on lung surfactant are now under way under our sponsorship or that of the A.M.A.E. R.F., I cannot easily judge whether our Board will feel that more is needed. It might depend on whether more promising methods or better experimental designs can be suggested.

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We are enclosing a copy of the recent paper by Torbjorn Lundman. It presents very cogent evidence of the genetic influence in coronary heart disease as compared to environmental ones.

Meanwhile progress is being made in the study of how other habits and practises tend to "cluster" with cigarette smoking. Mr. Kurt Enslein, who is applying multivariate analysis to large bodies of descriptive data from epidemiological studies expresses this by saying that "smoking and drinking appear to be summarizing other and perhaps unmeasured variables". In terms of such variables, he is attempting to "describe" the smoker as compared to the non-smoker.

We hope that the combination of data from such more sophisticated epidemiological studies and experimental ones will produce some definite answers in time.

With kind regards,

Sincerely yours,

Robert C. Hockett, Ph.D.
Associate Scientific Director

P.S. We enclose three sets of our revised application form. The next logical target date will be the September meeting of our Scientific Advisory Board. The deadline is August first but earlier receipt is an advantage since it spreads out the Board's work load.

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